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ATTORNEY DOCKET NO. **10992786-1**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Jeffery R. Sampson et al.

Serial No.: 09/632,639 **Examiner: Zara, Jane J.**

Filing Date: July 31, 2000 **Group Art Unit: 1635**

Title: Inhibition of Target-Mediated Cross-Hybridization

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☒ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

☐	one month	$ 120.00
☐	two months	$ 450.00
☐	three months	$1020.00
☒	four months	$1590.00

☐ The extension fee has already been filled in this application.

☐ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $2090.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078** pursuant to 37 CFR 1.25.

A duplicate copy of this transmittal letter is enclosed.

☒ I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Typed Name: Jennifer Pomonis

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Respectfully submitted,

Jeffery R. Sampson et al.

By Cynthia J. Lee

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Reg. No. 46, 033

Date: May 4, 2005

Telephone No. 770-933-9500

Rev 10/04 (AplBrief)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of:

Jeffery R. Sampson *et al.*

Confirmation No.: **3760**

Group Art Unit: **1635**

Serial No.: **09/632,639**

Examiner: **Zara, Jane J.**

Filed: **July 31, 2000**

Docket No.: **10992786-1**

For: **Inhibition of Target-Mediated Cross-Hybridization**

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Mail Stop Appeal Brief - Patents; Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on May 5, 2005

J. Pomonis

Signature – Jennifer Pomonis

APPEAL BRIEF UNDER 37 C.F.R. §41.37

Mail Stop: Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Sir:

This Appeal Brief under 37 C.F.R. §41.37 is submitted in triplicate in support of the Notice of Appeal filed November 5, 2004, responding to the Final Office Action mailed May 5, 2004 (Paper No. 20040420).

It is not believed that extensions of time or fees are required to consider this Appeal Brief, beyond those that have otherwise been provided for herein. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. §1.136(a), and any fees required therefor are hereby authorized to be charged to Deposit Account No. 03-1721

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I. REAL PARTY IN INTEREST

The real party in interest of the instant application is Agilent Technologies, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no other related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-26 are currently pending in the application. The rejection of all claims 1-26 is currently appealed. Claims 1-3, 5, 8-9, 11-12, 14-15, 17, 20-21, and 23-24 have been amended during the prosecution of this application. The remaining claims remain pending in their original form.

The Final Office Action mailed May 5, 2005, rejected claims 1-5, 7-17, and 19-26 under 35 U.S.C. §102(e) as allegedly being unpatentable over U.S. Patent No. 6,569,630 issued to *Vivekananda* et al. (hereinafter "*Vivekananda et al.*"). Additionally, the Final Office Action rejected claims 1-26 in view of U.S. Patent No. 5,912,340 issued to *Kutyavin* et al. (hereinafter "*Kutyavin et al.*").

For the reasons set forth herein, Applicants respectfully submit that the Board of Patent Appeals should overturn the rejection of pending claims 1-26.

IV. STATUS OF AMENDMENTS

Applicants submitted a Response to the Final Office Action on November 5, 2004, in which claims 1, 3, 5, 8, 10, 11, 12, 13, 15, 17, 20, 23, and 24 were amended. In an Advisory Action issued December 20, 2004, Applicants were advised that none of the amendments made after the Final Office Action would be entered. Therefore, the claims are pending in the format presented in the Appendix herein.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is directed to methods of enzymatically producing nucleic acids using nucleotide precursors that include at least one pair of complementary precursors, *e.g.*, "C" and "G" analogs or "A" and "T" analogs, where the complementary precursors have a reduced ability to base pair with each other but can still base pair with their complementary naturally occurring nucleotides. *See Specification* at *e.g.*, page16, lines 7-24 and page 19, lines 4-5. Thus, in one embodiment of the disclosed methods, for example, among others, in a modified sequence element, one or both of the nucleotides that together form an complementary base pair is substituted with a nucleotide containing a base analog so that the base pair is no longer formed, or is only formed at a reduced level. Preferably, the reduced level of base pairing is no more than one hydrogen bond interaction. Preferably, the analog(s) is selected so that the sequence element retains the ability to hybridize with a third sequence element in a nucleic acid molecule of complementary or substantially complementary sequence. *Id.* at page 17, lines 5-11.

The base pairing concepts of the present disclosure are schematically depicted by the following formulas where A' ≠ T' and G' ≠ C' represent disallowed base-pairing schemes, with the symbol ≠ representing the inability to form a base pair. [A*, T*, G*, and C*] represent a second group of bases capable of forming base pairs with A', T', G' and C' according to the general Watson-Crick base pair scheme of A=T and G=C, where = represents the ability to form a base pair. The same base pairing rules apply for RNA where U replaces T. (The horizontal base pairing symbols are not meant to represent the number of hydrogen bonds present in the base pair, but are meant only to indicate a stable base pair or lack of a stable base pair.)

$$(A' \neq T';\ G' \neq C') \qquad (1)$$

$$(A'=T^*;\ T'=A^*;\ G'=C^*;\ C'=G^*) \qquad (2)$$

Formula 1 indicates that base pair analogs A'/T' and G'/C' are unable to form a stable base pair. However, as indicated in Formula 2, the bases of nucleotides A', T', G', and C' are capable of forming stable base pairs with a second group of nucleotide bases (A*, T*, G*, and C*). *Id.* at page 17, lines 12-27.

The nucleic acids of the claims may contain a mixture of nucleotide analogs and naturally-occurring nucleotides. The nucleic acids of the claims may also contain only

nucleotide base analogs. More specifically, in accordance with the base pairing formulas outlined in Formula 1 and 2, nucleotides of the first group (A', T', G', and C') and nucleotides of the second group (A*, T*, G*, and C*) may include combinations of natural bases and modified bases or include all modified bases. For example, A' and T', which does not form a stable base pair, may be comprised of one nucleotide base analog (A') and one natural nucleotide (T'). Alternatively, A' and T' may be comprised of two nucleotide base analogs. Nucleotide pairs from the second group (e.g. A* and T*) may or may not form stable base pairs (A*=T* or A*≠T*). *Id.* at page 17, line 28 - page 18, line 8.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues in this appeal include the following: (1) whether claims 1-26 are unpatentable under 35 U.S.C. §102(e) over *Vivekananda et al.*; and (2) whether claims 1-26 are unpatentable under 35 U.S.C. §102(e) over *Kutyavin et al.*

VII. ARGUMENT

Applicants respectfully submit that claims 1-26 are novel under 35 U.S.C. § 102(e). Applicants respectfully request that the Board of Patent Appeals overturn the final rejections of those claims for the reasons discussed below.

A. Claims 1-5, 7-17, and 19-26 are novel under 35 U.S.C. §102(e) over *Vivekananda et al.*

Applicants respectfully submit that claims 1-5, 7-17, and 19-26 are patentable in view of *Vivekananda et al.*

1. Rejections

The following is a synopsis of the outstanding rejections that are appealed.

a. First Office Action

The first Office Action mailed October 2, 2003, the substance of which was reiterated in the Final Office Action of May 5, 2004, with respect to claim 1-5, 7-17, and 19-26, states as follows:

> *Vivekananda et al.* teach methods and compositions (e.g. kits) comprising synthesizing nucleic acid molecules with reduced levels of cross hybridization (see col. 2, lines 20-65; col. 3, line 44-col. 5, line 67; col. 6, line 62-col. 10, line 31), which synthesizing comprises the polymerization of nucleotide precursors form a DNA or RNA template by an appropriate polymerase or transcriptase (see col. 22, line 29-col. 24, line 45), and which nucleotide precursors include 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine 5'-triphosphate, and inosine triphosphate (see col. 20, line 14-col. 22, line 9), whereby a nucleic acid molecule with reduced levels of cross-hybridization is synthesized.

First Office Action at 5-6. Applicants traverse this rejection.

b. Final Office Action and Advisory Action

The Final Office Action of May 5, 2004, states as follows:

> *Vivekananda* teaches methods of synthesizing nucleic acid molecules comprising the incorporation of nucleotide analog precursors with a reduced ability to form base pairs with each other (e.g. 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine 5'-triphosphate...) employing such enzymes known in art as polymerases, as claimed in the instant invention. It is unclear what is meant in Applicants' arguments by *specifically employing a pair of nucleotide analogs*, that distinguishes the instant invention from the prior art. It was well known in the art and taught by *Vivekananda* that these nucleotide analogues are incorporated into polynucleotides by enzymes such as polymerases, and it was well known in the art that these analogues have a reduced ability to hybridize to complementary analogues (e.g. because of reduced hydrogen bonding between analogues), compared to non-analogue containing complementary base pairing. The claims are not drawn to a method of specifically employing a pair of nucleotide analogs, as suggested in Applicants' arguments, but instead are drawn to a method of synthesizing nucleic acid molecules that incorporate the nucleotide analogs into a polynucleotide, which analogues are characterized by their reduced ability to hybridize with complementary analogues.

Final Office Action at 2-3 (emphasis in original). Applicants traverse these assertions.

Additionally, the Advisory Action issued on December 20, 2004, states as follows:

> *Vivekananda et al.* teach the synthesis of the nucleic acid molecules claimed: See col. 20, line 13-col. 25, line 4, where *Vivekananda et al.* teach the

> synthesis of nucleic acid molecules, e.g. comprising "the synthesis of a nascent nucleic acid in a template-dependent process..." (e.g. col. 22, lines 20-28). These nascent nucleic acid molecules optionally incorporate "exemplary purine and pyrimidine derivatives and mimics" as provided in Table 1, col. 20-21, and include the nucleotide precursors identical to those of the instantly claimed methods. The methods of making nascent nucleic acid molecules described by *Vivekananda et al.* therefore anticipate those of the instantly claimed invention and, contrary to Applicants' assertions, the nucleic acid molecules synthesized, using the same methods as instantly claims, also inherently possess the same characteristics of the nucleic acids claimed.

Advisory Office Action at 2-3. Applicants also traverse these assertions.

2. *Vivekananda et al.* Do Not Teach or Suggest Each of the Features of the Claims

Claims 1-5, 7-17, and 19-26 recite steps/features that are not taught or suggested by the *Vivekananda et al.* reference. Thus, *Vivekananda et al.* do not anticipate claims 1-5, 7-17, and 19-26.

a. Case Law of 35 U.S.C. §102(e)

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987). *See also Scripps Clinic and Research Found. v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

b. Claims 1, 12, and 24

Independent claims 1, 12, 24 are not anticipated by *Vivekananda et al.* because they recite features that are not taught or suggested by the reference.

Upon careful review of the *Vivekananda et al.* reference, including the specific sections cited by the Examiner, no teaching can be found of any method where one must specifically **employ a pair of nucleotide analogs**, as claimed in the presently claimed

methods. Specifically, claim 1 recites "a method of synthesizing nucleic acid molecules comprising steps of: ... providing nucleotide precursors that include at least one pair of complementary **nucleotide analog** precursors that have a reduced ability to form base pairs with each other...." *Claim 1* (emphasis added). The *Vivekananda et al.* reference at least fails to teach this element of the claimed methods and kit.

Additionally, contrary to the Examiner's assertion in the Final Office Action, *Vivekananda et al.* also does not teach methods of synthesizing nucleic acid molecules with reduced levels of cross hybridization. *Vivekananda et al.* disclose a method of detecting anthrax spores and other chemical and biological agents. They achieve this by utilizing nucleic acid molecules that are able to specifically bind particular targets, preferable through non-Watson-Crick interactions. Specifically, *Vivekananda et al.* define their preferred nucleic acid aptamers as a "nucleic acid that binds to another molecule ('target' as defined below). *This binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation exemplified by Watson-Crick basepair formation (e.g., A binds to U or T and G binds to C), but encompasses all other types of non-covalent (or in some cases covalent) binding."* Column 8, lines 27-33 (emphasis added). The intended binding target of *Vivekananda et al.'s* nucleic acids are "any compound or aggregate of interest. Non-limiting examples include a protein, peptide, carbohydrate, polysaccharide, glycoprotein, lipid, hormone, receptor, antigen, allergen, antibody, substrate, metabolite, cofactor, inhibitor, drug, pharmaceutical, nutrient, toxin, cholera toxin, Shiga-toxin, poison, explosive pesticide, chemical warfare agent, biohazardous agent, prion, radioisotope, vitamin, heterocyclic aromatic compound, carcinogen, mutagen, narcotic, amphetamine, barbiturate, hallucinoge, waste product, contaminant, or other molecule." Column 8, lines 46-56. Thus, *Vivekananda et al.* do not teach a method of synthesizing nucleic acids with reduced levels of cross hybridization, but instead teach a method of synthesizing nucleic acids that bind to their

intended non-nucleic acid targets with greater affinity via non-Watson-Crick-type interactions.

By contrast, Claim 1, for example, is directed to a method of synthesizing nucleic acid molecules that includes "providing **nucleotide precursors** that include at least one pair of complementary nucleotide precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide." Similar language is found in independent claims 12 and 24. Thus, the presently pending claims recite the synthesis of nucleic acid molecules that **do** bind to certain nucleic acid molecules via traditional Watson-Crick-like hydrogen bonding interactions (*i.e.*, "each member of said pair can form a base pair with its complementary naturally occurring nucleotide" of claim 1). *Vivekananda et al.* simply do not teach or suggest such a method. Instead, by stating that their invention "does not encompass standard nucleic acid/nucleic acid hydrogen bond formation" (col. 8, lines 28-20), *Vivekananda et al.* actually teach away from the currently pending claims, and thus cannot anticipate the present claims.

Because *Vivekananda et al.* at least fail to teach these element of the claims, independent claims 1, 12, and 24 are not anticipated under 35 U.S.C. § 102(e) by *Vivekananda et al.* Applicants respectfully request that the Board overturn the rejection.

c. Claims 3 and 15

Claim 3 recites "the precursors contain A' and T' wherein A' and T' have a reduced ability to form a stable hydrogen-bonded base pair, wherein A' can form a stable base pair with T* and wherein T' can form a stable base pair with A*." Claim 15 has identical language. As noted above, *Vivekananda et al.* teach that "*[t]his binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation exemplified by*

Watson-Crick basepair formation (e.g., A binds to U or T and G binds to C), but encompasses all other types of non-covalent (or in some cases covalent) binding." Column 8, lines 27-33 (emphasis added). Thus, the recited feature of claims 3 and 15 is clearly not anticipated by *Vivekananda et al.* Applicants submit that for at least this reason, the rejection of claims 3 and 15 based on *Vivekananda et al.* should be overturned.

Additionally, as a separate and independent basis for traversing the rejections, pending dependent claims 3 and 15 contain all features of their respective independent claims 1 and 12. Since claims 1 and 12 should be allowed, as argued above, pending dependent claims 3 and 15 should be allowed as a matter of law for at least this reason. *In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). Applicants respectfully request that the rejections of these claims be overturned as well by the Board.

d. Claims 5 and 17

Claim 5 recites "the precursors contain G' and C' wherein G' and C' have a reduced ability to form a stable hydrogen-bonded base pair, wherein G' can form a stable base pair with C*, and wherein C' can form a stable base pair with G*." Claim 17 has identical language. As noted above, *Vivekananda et al.* teach that *"[t]his binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation exemplified by Watson-Crick basepair formation (e.g., A binds to U or T and G binds to C), but encompasses all other types of non-covalent (or in some cases covalent) binding."* Column 8, lines 27-33 (emphasis added). Thus, the recited feature of claims 5 and 17 is clearly not anticipated by *Vivekananda et al.* Applicants submit that for at least this reason, the rejection of claims 5 and 17 based on *Vivekananda et al.* should be overturned.

Additionally, as a separate and independent basis for traversing the rejections, pending dependent claims 5 and 17 contain all features of their respective independent claims 1 and 12. Since claims 1 and 12 should be allowed, as argued above, pending dependent claims 5 and 17

should be allowed as a matter of law for at least this reason. Applicants respectfully request that the rejections of these claims be overturned as well by the Board.

e. Claims 11 and 23

Claim 11 recites "at least one nucleotide precursor having a purine analog and at least one nucleotide having a pyrimidine analog wherein the purine analog and the pyrimidine analog are not capable of forming a stable hydrogen bonded base pair, and wherein at least one of the purine or pyrimidine analogs is capable of forming a stable hydrogen bonded base pair with another complementary analog or complementary natural base." Claim 23 has identical language. Applicants submit that *Vivekananda et al.* specifically teach away from this feature. For at least this reason, the rejection of claims 11 and 23 based on *Vivekananda et al.* should be overturned.

Additionally, as a separate and independent basis for traversing the rejections, pending dependent claims 11 and 23 contain all features of their respective independent claims 1 and 12. Since claims 1 and 12 should be allowed, as argued above, pending dependent claims 11 and 23 should be allowed as a matter of law for at least this reason. Applicants respectfully request that the rejections of these claims be overturned as well by the Board.

f. Claims 2, 4, 7-10, 13-14, 16, 19-22, and 25-26

Additionally, as a separate and independent basis for traversing the rejections, pending dependent claims 2, 4, 7-10, 13-14, 16, 19-22, and 25-26 contain all features of their respective independent claims 1, 12, and 24. Since claims 1, 12, and 24 should be allowed, as argued above, pending dependent claims 2, 4, 7-10, 13-14, 16, 19-22, and 25-26 should be allowed as a matter of law for at least this reason. *In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

Applicants respectfully request that the rejections of these claims be overturned as well by the Board.

B. Claims 1-26 are novel under 35 U.S.C. §102(e) over *Kutyavin et al.*

Applicants respectfully submit that claims 1-26 are patentable in view of *Kutyavin et al.*

1. Rejections

a. First Office Action

The first Office Action mailed October 2, 2003, the substance of which was reiterated in the Final Office Action of May 5, 2004, with respect to claim 1-5, 7-17, and 19-26, states as follows:

> *Kutyavin et al.* teach methods and compositions (e.g. kits) comprising synthesizing nucleic acid molecules with reduced levels of cross hybridization (see the abstract; col. 2, line 33-col. 9, line 53; claims 1-20, 23-25), which synthesizing comprises the polymerization of nucleotide precursors form a DNA or RNA template by an appropriate polymerase or transcriptase, (see col. 18 and 22-23), and which nucleotide precursors include 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine or –cytidine, 5'-triphosphate, pyrrolo-pyrimidine triphosphate, inosine triphosphate (see col. 5, col. 34, lines 53-67), whereby a nucleic acid molecule with reduced levels of cross-hybridization is synthesized (see abstract; text in col. 4; claims 1-20).

First Office Action at 6. Applicants traverse this rejection.

b. Final Office Action and Advisory Action

The Final Office Action of May 5, 2004, states as follows:

> *Kutyavin* teaches methods of synthesizing nucleic acid molecules comprising the incorporation of nucleotide analog precursors with a reduced ability to form base pairs with each other (e.g. 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine or cytidine 5'-triphoshate, pyrrolo pyrimidine triphosphate, inosine triphosphate...) employing such enzymes known in art as polymerases, as claimed in the instant invention. It is unclear what is meant in Applicants' arguments by *specifically employing a pair of nucleotide analogs*, that distinguishes the instant invention from the prior art. It was well known in art and taught by *Kutyavin et al.* that these nucleotide analogues are incorporated into polynucleotides by enzymes such as

> polymerases, and it was well known in the art that these analogues have a reduced ability to hybridize to complementary analogues (e.g. because of reduced hydrogen bonding between analogues), compared to non-analogue containing complementary base pairing. The claims are not drawn to a method of specifically employing a pair of nucleotide analogs, as suggested in Applicants' arguments, but instead are drawn to a method of synthesizing nucleic acid molecules that incorporate the nucleotide analogs into a polynucleotide, which analogues are characterized by their reduced ability to hybridize with complementary analogues.

Final Office Action at 3-4 (emphasis in original). Applicants traverse these assertions.

Additionally, the Advisory Action issued on December 20, 2004, states as follows:

> [T]he methods taught previously by *Kutyavin et al.*, of producing the nucleic acid strands comprising modified nucleotides within the nascent nucleic acid molecules are identical to those of the instant invention. Once the nucleic acid strands are produced by this method, it is a design choice to mix and match complementary strands containing either unmodified or modified nucleotides.

Advisory Office Action at 3. Applicants also traverse these assertions.

2. *Kutyavin et al.* Do Not Teach or Suggest Each of the Features of the Claims

Claims 1-26 are recite steps/features that are not taught or suggested by the *Kutyavin et al.* reference. Thus, *Kutyavin et al.* do not anticipate claims 1-26.

a. Case Law of 35 U.S.C. §102(e)

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987). *See also Scripps Clinic and Research Found. v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

b. Claims 1, 12, and 24

Independent claims 1, 12, 24 are not anticipated by *Kutyavin et al.* because they recite features that are not taught or suggested by the reference.

Upon careful review of the *Kutyavin et al.* reference, including the specific sections cited by the Examiner, no teaching can be found of any method where one must specifically **employ a pair of nucleotide analogs**, as claimed in the presently claimed methods. Specifically, claim 1 recites "A method of synthesizing nucleic acid molecules comprising steps of: ... providing nucleotide precursors that include at least one pair of complementary **nucleotide analog** precursors that have a reduced ability to form base pairs with each other...." *Claim 1* (emphasis added). The *Kutyavin et al.* reference at least fails to teach this element of the claimed methods and kit.

Additionally, *Kutyavin et al.* disclose a matched set of oligonucleotides containing modified nucleotides such that each member of the matched set is able to hybridize with a complementary strand in a duplex nucleic acid molecule, but is unable to hybridize with the other member of the matched set. The disclosure of *Kutyavin et al.* addresses the specific problem of facilitating strand invasion of a duplex nucleic acid molecule (see col. 1, lines 15-36) since the matched set of complementary oligonucleotides will not bind each other. Thus, each member of the matched set will be available to invade a duplex nucleic acid molecule. The key feature disclosed by *Kutyavin et al.* is that the matched set of oligonucleotides must be unable to base pair with each other (see col. 1, lines 51-53, "Thus, the matched pair of oligonucleotides in accordance with the present invention do not form substantially stable hydrogen bonded hybrids with *one another*..." (emphasis added)). However, *Kutyavin et al.* do not teach or suggest a method of producing nucleic acid molecules that contain pairs of nucleotides such that the nucleic acid molecules: 1) are unable to base pair with each other, and 2) are individually unable to form intramolecular base pair interactions. In contrast, the

currently pending claims recite a method of producing a nucleic acid molecules that not only have a reduced ability to form stable hydrogen bonded base pairs with each other, but also have a reduced ability to form stable hydrogen bonded intramolecular base pair interactions.

The reduced ability of the molecules produced in accordance with the present claims to form both intermolecular and intramolecular hydrogen bonded base pairs stems from the fact that both members of a non-hydrogen bond forming nucleotide pair are necessarily present in each nucleic acid molecule produced. For example, independent claim 1 recites a method of synthesizing nucleic acid molecules by providing a collection of nucleotides that includes "at least one pair of complementary nucleotides that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide" (emphasis added). Similarly, independent claims 12 recites a method of producing nucleic acid molecules by providing a collection of nucleotides that includes "pairs of complementary nucleotides that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide" (emphasis added). The matched set of oligonucleotides disclosed in *Kutyavin et al.* contains no such limitation and thus cannot anticipate the currently pending claims.

Because *Kutyavin et al.* at least fails to teach these element of the claims, independent claims 1, 12, and 24 are not anticipated under 35 U.S.C. § 102(e) by *Kutyavin et al.* Applicants respectfully request that the Board overturn the rejection.

c. Claims 2-5, 7-11, 13-17, 19-23, and 25-26

Additionally, as a separate and independent basis for traversing the rejections, pending dependent claims 2-5, 7-11, 13-17, 19-23, and 25-26 contain all features of their respective independent claims 1, 12, and 24. Since claims 1, 12, and 24 should be allowed, as argued

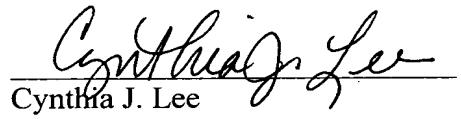
above, pending dependent claims 2-5, 7-11, 13-17, 19-23, and 25-26 should be allowed as a matter of law for at least this reason. Applicants respectfully request that the rejections of these claims be overturned as well by the Board.

CONCLUSION

In view of the foregoing, it is believed that all pending claims 1-26 are in proper condition for allowance, and the Board is respectfully requested to overturn each of the Examiner's rejections of each of these claims.

Respectfully submitted,

THOMAS, KAYDEN, HORSTEMEYER & RISLEY, L.L.P.



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VIII. CLAIMS APPENDIX

1. A method of synthesizing nucleic acid molecules comprising steps of:

a) providing at least one nucleic acid template;

b) providing nucleotide precursors that include at least one pair of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide; and

c) contacting the template and nucleotide precursors with an enzyme characterized by an ability to polymerize the precursors under conditions and for a time sufficient for synthesis of the nucleic acid molecule.

2. The method of claim 1, wherein in the step of providing a template, the template is RNA, messenger RNA, DNA, genomic DNA, plasmid DNA or DNA reverse transcribed from RNA.

3. The method of claim 1, wherein in the step of providing nucleotide precursors, the precursors contain A' and T' wherein A' and T' have a reduced ability to form a stable hydrogen-bonded base pair, wherein A' can form a stable base pair with T* and wherein T' can form a stable base pair with A*.

4. The method of claim 3, wherein A' is 2-aminoadenosine triphosphate, T' is 2-thiothymidine triphosphate, A* is adenine and T* is thymidine.

5. The method of claim 1, wherein in the step of providing nucleotide precursors, the precursors contain G' and C' wherein G' and C' have a reduced ability to form a stable hydrogen-bonded base pair, wherein G' can form a stable base pair with C*, and wherein C' can form a stable base pair with G*.

6. The method of claim 5, wherein G' is inosine triphosphate, C' is pyrrolo-pyrimidine triphosphate, G* is guanosine and C* is cytidine.

7. The method of claim 5, wherein G' is guanosine triphosphate, C' is 2-thioC triphosphate, G* is inosine triphosphate and C* is cytidine triphosphate.

8. The method of claim 1, wherein in the step of providing nucleotide precursors, the precursors are selected from the group consisting of: 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine 5'-triphosphate, deoxyinosine 5'-triphosphate, deoxypyrrolopyrimidine 5'-triphosphate, 2-thiodeoxycytidine 5'-triphosphate, deoxyguanosine 5'-triphosphate, deoxycytidine 5'-triphosphate, deoxyadenosine 5'-triphosphate, deoxythymidine 5'-triphosphate, and combinations thereof.

9. The method of claim 1, wherein in the step of contacting, the enzyme is selected from the group consisting of: RNA polymerase, DNA polymerase, reverse transcriptase, ribozyme, and self-replicating RNA molecule.

10. The method of claim 1, wherein the nucleic acid molecules with reduced levels of cross hybridization are used in a ligase assay, a polymerase extension assay, or a nucleic acid array assay.

11. The method of claim 1, wherein the step of providing nucleotide precursors comprises providing at least one nucleotide precursor having a purine analog and at least one nucleotide having a pyrimidine analog wherein the purine analog and the pyrimidine analog are not capable of forming a stable hydrogen bonded base pair, and wherein at least one of the purine or pyrimidine analogs is capable of forming a stable hydrogen bonded base pair with another complementary analog or complementary natural base.

12. A method of producing nucleic acid molecules comprising steps of:

a) providing a first nucleic acid template having a first sequence element;

b) providing a second nucleic acid template having a second sequence element, wherein the second sequence element is substantially complementary to the first sequence element;

c) providing nucleotide precursors that include pairs of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide;

d) contacting the first template and nucleotide precursors with an enzyme characterized by an ability to polymerize the precursors under conditions and for a time sufficient for synthesis of the first nucleic acid molecule; and

e) contacting the second template and nucleotide precursors with an enzyme characterized by an ability to polymerize the precursors under conditions and for a time sufficient for synthesis of the second nucleic acid molecule, wherein at least one of the nucleic acid molecules synthesized is characterized by an ability to hybridize to a third nucleic acid molecule.

13. The method of claim 12, wherein the step of contacting the first template and nucleotide precursors and the step of contacting the second template and nucleotide precursors are performed simultaneously in one reaction.

14. The method of claim 12, wherein in the step of providing a first template and wherein the step of providing a second template, the templates are selected from the group consisting of: RNA, messenger RNA, DNA, genomic DNA, plasmid DNA or DNA reverse transcribed from RNA.

15. The method of claim 12, wherein in the step of providing nucleotide precursors, the precursors contain A' and T' wherein A' and T' have a reduced ability to form a stable hydrogen-bonded base pair with each other, wherein A' can form a stable base pair with T* and wherein T' can form a stable base pair with A*.

16. The method of claim 15, wherein A' is 2-aminoadenosine triphosphate, T' is 2-thiothymidine triphosphate, A* is adenosine and T* is thymidine.

17. The method of claim 12, wherein in the step of providing nucleotide precursors, the precursors contain G' and C' wherein G' and C' have a reduced ability to form a stable hydrogen-bonded base pair, wherein G' can form a stable base pair with C*, and wherein C' can form a stable base pair with G*.

18. The method of claim 17, wherein G' is inosine triphosphate, C' is pyrrolo-pyrimidine triphosphate, G* is guanosine and C* is cytidine.

19. The method of claim 17, wherein G' is guanosine triphosphate, C' is 2-thioC triphosphate, G* is inosine and C* is cytidine.

20. The method of claim 12, wherein in the step of providing nucleotide precursors, the precursors are selected from the group consisting of: 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine 5'-triphosphate, deoxyinosine 5'-triphosphate, deoxypyrrolopyrimidine 5'-triphosphate, 2-thiodeoxycytidine 5'-triphosphate, deoxyguanosine 5'-triphosphate, deoxycytidine 5'-triphosphate, deoxyadenosine 5'-triphosphate, deoxythymidine 5'-triphosphate, and combinations thereof.

21. The method of claim 12, wherein in the step of contacting, the enzyme is selected from the group consisting of: RNA polymerase, DNA polymerase, reverse transcriptase, ribozyme, and self-replicating RNA molecule.

22. The method of claim 12, wherein the nucleic acid molecules are used in a ligase assay, a polymerase extension assay, or a nucleic acid array assay.

23. The method of claim 12, wherein the step of providing nucleotide precursors comprises providing at least one nucleotide precursor having a purine analog and at least one nucleotide having a pyrimidine analog wherein said purine analog and said pyrimidine analog are not capable of forming a stable hydrogen bonded base pair, and wherein at least one of the purine or pyrimidine analogs is capable of forming a stable hydrogen bonded base pair with another complementary analog or complementary natural base.

24. A kit comprising:

nucleotide precursors that include pairs of complementary nucleotide analog precursors that have a reduced ability to form base pairs with each other, wherein each member of said pair can form a base pair with its complementary naturally occurring nucleotide; and

at least one enzyme capable of polymerizing the precursors into a polynucleotide molecule

25. (Original) The kit of claim 24 comprising an enzyme capable of polymerizing nucleotide precursors into a polynucleotide molecule, buffer solutions, and nucleotide

precursors selected from the group consisting of: 2-aminodeoxyadenosine 5'-triphosphate, 2-thiodeoxythymidine 5'-triphosphate, deoxyinosine 5'-triphosphate, deoxypyrrolopyrimidine 5'-triphosphate, 2-thiodeoxycytidine 5'-triphosphate, deoxyguanosine 5'-triphosphate, deoxycytidine 5'-triphosphate, deoxyadenosine 5'-triphosphate, deoxythymidine 5'-triphosphate.

26. The kit of claim 24, wherein the enzyme is selected from the group consisting of: RNA polymerase, DNA polymerase, reverse transcriptase, ribozyme, and self-replicating RNA molecule.